

AD _____

Award Number: DAMD17-99-1-9498

TITLE: SPECT and fMRI Analysis of Motor and Cognitive Indices of
Early Parkinson's Disease: The Relationship of Striatal
Dopamine and Cortical Function

PRINCIPAL INVESTIGATOR: John D.E. Gabrieli, Ph.D.

CONTRACTING ORGANIZATION: Rush-Presbyterian-St. Luke's
Medical Center
Chicago, Illinois 60612

REPORT DATE: October 2000

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are
those of the author(s) and should not be construed as an official
Department of the Army position, policy or decision unless so
designated by other documentation.

20011116 128

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 074-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503				
1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE October 2000		3. REPORT TYPE AND DATES COVERED Annual (1 Oct 99 - 30 Sep 00)
4. TITLE AND SUBTITLE SPECT and fMRI Analysis of Motor and Cognitive Indices of Early Parkinson's Disease: The Relationship of Striatal Dopamine and Cortical Function			5. FUNDING NUMBERS DAMD17-99-1-9498	
6. AUTHOR(S) John D.E. Gabrieli, Ph.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Rush-Presbyterian-St. Luke's Medical Center Chicago, Illinois 60612 E-Mail: gabrieli@psych.stanford.edu			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited				12b. DISTRIBUTION CODE
13. ABSTRACT (Maximum 200 Words)				
14. SUBJECT TERMS Neurotoxin			15. NUMBER OF PAGES 13	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

Table of Contents

Cover.....	i
SF 298.....	ii
Table of Contents.....	iii
Introduction.....	1
Body.....	2
Appendices.....	

RUSH-PRESBYTERIAN-ST.LUKE'S MEDICAL CENTER

Department of Neurological Sciences

Section of Movement Disorders

Harold L. Klawans, M.D. - Founder

Christopher G. Goetz, M.D. - Director

Cynthia L. Comella, MD
Katie Kompoliti, MD
Kathleen M. Shannon, MD
Leo Verhagen, MD

Bryan Bernard, PhD
Glenn T. Stebbins, PhD
Luci Blasucci, RN
Jean A. Jaglin, RN

Kimberly Janko, BSN
Teresa Chmura
Bernadette Gilard
Marilynn Payton

Glenn T. Stebbins, Ph.D.

Ms. Judy Pawlus
Office of the Deputy Chief of Staff for Information
Management
U.S. Army Medical Research and Materiel Command
504 Scott Street
Fort Detrick, MD 21702-5012

Re: Annual Report for Award Number DAMD17-99-1-9498

December 19, 2000

Dear Ms. Pawlus:

I apologize for the tardiness of this Annual Report, but as I explained we had requested an Extension Without Funds, and had assumed this would push back the date of our required submission.

Progress Report for DAMD17-99-1-9498

The goals for the first funding period of this award were as follows:

1. **Initial set up and identification of patient and control participants (2 months)**
 - Identification of participants required for the first year of project
 - Preparation of forms for behavioral testing
 - Scheduling needed time at MRI Clinic and SPECT Radiology
 - Schedule preparation of ligand with pharmaceutical company
- 1a. **Data collection and analysis (10 months)**
 - At least 45 participants identified from our cohort of PD, HA, and YNC will be scheduled for the three visits required, behavioral, fMRI, and SPECT
 - Recruitment and enrollment will continue for additional participants
 - Analysis of behavioral data collected in this time period will be scored
 - Analysis of fMRI data and SPECT data will be analyzed and co-registered
 - Annual progress report requested by sponsor will be completed
 - An abstract will be prepared for the Society for Neuroscience Conference

Goals 1: Initial set up and identification of patients and control participants

We have met the goals for #1. Through the efforts of Dr. David Bennett and a Nurse Coordinator we had examined the database of available subjects in the Memory Assessment Project and the Section of Movement Disorder in the Department of Neurological Sciences at Rush-Presbyterian-St. Luke's Medical Center. From this list we have identified 63 potential participants for the first year of the project. Examination of these sources for additional participants continues and will yield sufficient numbers of participants to meet the overall recruitment goals of the project. We have not recruited any subjects to date because we are awaiting final approval from the Office of Regulatory Compliance and Quality at the USAMRMC.

The delay experienced at the USAMRMC-RCQ during 1999 and early 2000 resulted in our loss of use of the proposed SPECT ligand (^{123}I β -CIT) due to a discontinuation of production at Guildford Pharmaceuticals. We received the discontinuation notice from the manufacturer in February of 2000. We were able to identify a newly developed, superior ligand (^{123}I Altoprane) manufactured by Boston Life Sciences, Inc. This new ligand is superior to ^{123}I β -CIT in a number of areas. First, the new ligand reaches binding constant to the dopamine active transporter (DAT) in 45 minutes as opposed to 24 hours as was true for ^{123}I β -CIT. This means participants can receive SPECT scanning in a single visit as opposed to two separate visits (one for injection of the ligand and a second visit 24 hours later for SPECT scanning). Second, the new ligand shows a higher affinity to DAT than ^{123}I β -CIT and does not show cross binding with other monoaminergic receptors. Third, the radiation exposure to participants is lower with the new ligand as opposed to ^{123}I β -CIT thus lowering such potential risks.

The use of a new radioactive ligand required our submission to the Food and Drug Administration for a new IND, which was awarded on October 14, 2000 (see Attachment A). In addition, we were required to seek approval from our institutional Radiation Safety Committee for a new Authorization License Number. This approval was received on November 28, 2000 (see Attachment B). Finally, we had to seek re-approval from our institution's Institutional Review Board for Human Subjects Research. This approval was received on November 1, 2000 (see Attachment C). The USAMRMC-RCQ is currently reviewing the modified protocol, FDA approval, Radiation Safety Committee approval, and Institutional Review Board approval in order to issue its final approval to begin the recruitment and testing of participants.

In the interim we have developed all required forms and testing material for behavioral and motor testing of subjects. We have developed and piloted the experiments that will be used during functional MRI scanning. Finally, arrangements had been in place with the Department of Diagnostic Radiology Sections of Nuclear Medicine and Magnetic Resonance Imaging for the scheduling and examination of participants.

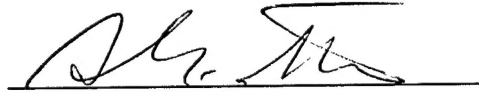
Goal 1a: Data collection and analysis

We cannot enroll any participants until we receive final approval from the USAMRMC-RCQ. However, we have made some progress on Goal 1a. We had developed and tested the analytic techniques for combining different imaging data types, including co-registration of structural, functional and diffusion weighted imaging, normalization of brain images to a common atlas, and statistical analyses of the resultant data. These procedures are in place and will be easily implemented when we acquire our data.

Due to the delays listed above, we sought approval for a ten month Extension Without Funds from the office of Sacelia Heller, Contract Specialist, U.S. Army Medical Research Acquisition Activity. We feel that ten months will allow sufficient time to recover from the delay in enrolling and testing of the first year's cohort of participants.

We are anxious to start enrolling and testing participants and await the final approval from the USAMRMC-RCQ Committee. If you have comments or questions regarding this Annual Progress Report, please contact me via mail (Glenn T. Stebbins, Ph.D., Department of Neurological Sciences, Rush-Presbyterian-St. Luke's Medical Center, 1645 W. Jackson, Suite 450, Chicago, IL 60612), telephone ((312)432-5033), or electronic mail (gstebbin@rush.edu).

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'G. T. Stebbins', is written over a horizontal line.

Glenn T. Stebbins, Ph.D.
Associate Professor of Neurological Sciences
Rush-Presbyterian-St. Luke's Medical Center

Attachment A – FDA approval



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 60,953

Amjad Ali, M.B.B.S.
Diagnostic Radiology and Nuclear Medicine
Rush-Presbyterian-St. Luke's Medical Center
1653 W. Congress Parkway
Chicago, IL 60612

Dear Dr. Ali:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for 123-I Altropane.

We have completed our 30-day safety review of your application and have concluded that you may proceed with your proposed clinical investigation.

If we have any comments to relay to you, we will send them to you in a separate letter.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

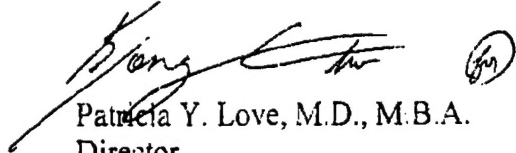
Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to the following address:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160
Attention: Division Document Room, 18B-06
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Tia Harper-Velazquez, Pharm.D., Regulatory Project Manager,
at (301) 827-7510.

Sincerely,

A handwritten signature in black ink, appearing to read "Patricia Y. Love", followed by a circled "for" in the right margin.

Patricia Y. Love, M.D., M.B.A.

Director

Division of Medical Imaging and

Radiopharmaceutical Drug Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

Attachment B – Radiation Safety Committee approval

RUSH-PRESBYTERIAN-ST. LUKE'S MEDICAL CENTER 1653 WEST CONGRESS PARKWAY, CHICAGO, ILLINOIS 60612



Date : November 28, 2000
To: Dr. Glenn T. Stebbins
Department : Neurological Sciences

From : Glenn P. Sullivan *GPS*
Radiation Safety Officer
Radiation Safety Office, 109 Jn
Ext. 25763 Pg: 85-7750

Re: Approval of Your Application for Use of Radioactive Material

Your application for the use of radioactive materials entitled: **SPECT and fMRI analysis of motor and cognitive indices of early Parkinson's disease: the relationship of striatal dopamine and cortical function**, has been reviewed and approved by the Radiation Safety and Radioisotope Committee on November 8, 2000 and has been assigned authorization license number **077**. This number must be used when ordering isotopes for this procedure through the Radiation Safety Office. The license restricts the use of the radioactive material to only the procedures and uses as stated therein, the isotope, chemical form, maximum purchase, on hand, and per experiment activities as stated, as well as procedures, safety requirements, specific disposal procedures, and lab location and facilities as specifically indicated in the application. Any variation in any of the above will require an amendment request or new application to be approved prior to any changes.

Proposed facility changes will require an amendment request giving the new location, new facility diagram, inspection, approval, and prior labeling of the lab by the radiation safety officer. It should include a request for decommissioning, final decontamination and survey of the prior facility, prior to its release to anyone as unrestricted.

The authorized user and workers under his supervision are required to observe all institutional rules and procedures only, for ordering, receiving, handling, and disposal of any radioactive material in order to be in compliance with all pertinent radiation regulations of the Statutes and Regulations, 32 Illinois Administrative Code of the State of Illinois Department of Nuclear Safety as well as license conditions. **The authorized user is responsible for the observance of all rules by his workers and their training in radiation safety procedures and handling techniques pertinent to the specific experimental procedure in this application. All radiation emergencies, radioactive spills, or other problems or irregularities must be immediately reported to the Radiation Safety Officer.**

Other Conditions: None

Your license will become active upon return of a copy of this form with your signature. This signature indicates that you are aware of the regulations and restrictions placed upon your use of radioactive material.

Authorized User Signature

Print Name & Title GLENN STEBBINS, Ph.D., Associate Professor

Date 11/30/00

THIS FORM MAY BE FAXED TO 2-2868.

C:\office\wpwin\wpdocs\license

Attachment C – IRB approval

RUSH-PRESBYTERIAN-ST. LUKE'S MEDICAL CENTER
1653 WEST CONGRESS PARKWAY, CHICAGO, ILLINOIS 60612-3833
RUSH UNIVERSITY



Institutional Review Board #1
(312) 942-5498

The following research activity has been re-reviewed and re-approved by the Institutional Review Board (IRB) at Rush-Presbyterian-St. Luke's Medical Center in accordance with the Common Rule (56FR28003, June 18, 1991) and any other governing regulations or subparts.

Principal Investigator: Stebbins, Glenn T., Ph.D

Project Title: SPECT and fMRI analysis of motor and cognitive indices of early parkinson's disease: the relationship of striatal dopamine and cortical function

DHHS Assurance ID No.: M1385

ORA No.: 99062901

Date of approval:

Due for continuing/annual review:

☒ Full Review or ☐ Expedited Review

Below is a list of your responsibilities related to this human subjects research project:

Conduct the study in accordance with the relevant, current protocol and only make changes in the protocol after notifying the IRB, except when necessary to protect the safety, rights or welfare of subjects.

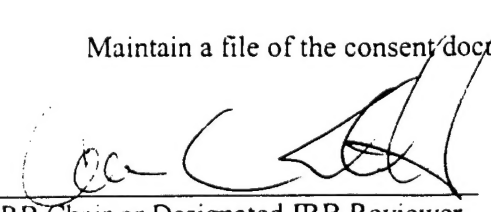
Record and track number of subjects accrued as well as information regarding study drop-outs or withdrawals.

Provide brief updates on the changing scientific literature as that literature pertains to the efficacy and safety of the specific procedure or intervention under study.

Report any complaints from subjects as well as any and all serious or unexpected adverse events related to this study to the IRB.

Maintain and use copies of the currently approved consent document related to this project.

Maintain a file of the consent documents bearing the signature of the subjects enrolled in this study.


IRB Chair or Designated IRB Reviewer


Date